

**ABSTRACT**

The invention provides methods for generating high titers of high-affinity antibodies from hybridoma cells produced by fusing myeloma cells with *in vitro* immunized donor cells. The hybridoma cells or mammalian expression cells with cloned antibody genes from the hybridomas producing the high-affinity antibodies may be mismatch repair defective due to defects of endogenous mismatch repair subunits or through expression of a dominant negative allele of a mismatch repair gene which allows the hybridoma cell to be hypermutable, may be rendered hypermutable by chemical means, or may be naturally mismatch repair deficient. High-affinity antibodies and high titer producer cells producing antibodies may be prepared by the methods of the invention.